# Defining the role of cancer-risk genes in Type 2 diabetes pathogenesis

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·To perform clinical studies that assess glucose tolerance in individuals with cancer-predisposing mutations in the CDKN2A gene (p16)(causing familial melanoma)

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON36169

**Source**
ToetsingOnline

**Brief title**
Cancer risk genes in type 2 diabetes pathogenesis

### Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

**Synonym**
diabetes mellitus; diabetes mellitus

**Health condition**

dragers van een p16-gen mutatie

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Medical research council UK; Diabetes UK

## Intervention

**Keyword:** cancer risk genes, CDKN2A (p16), type 2 diabetes

## Outcome measures

### Primary outcome

Do people with mutations in certain cancer*risk genes (CDKN2A) have altered

glucose tolerance.

### Secondary outcome

not applicable

# Study description

### Background summary

Over the past decade advances in genetics have resulted in considerable progress in defining the pathogenesis of type 2 diabetes. The discovery of several genes responsible for monogenic diabetes has given valuable insight into the workings of the beta-cell and its regulation. This work has had direct clinical impact through development of molecular diagnostic tools as well as more individualised therapy for patients based on their genetic diagnosis.
More recently genome wide association scans (GWAs) have uncovered some novel variants that predispose (albeit through individually modest effects) to the more common multifactorial type 2 diabetes.These discoveries are increasing our understanding of diabetes by implicating defects in previously unassociated pathways. One of the more interesting observations is that several of the genes which influence risk of diabetes also play a role in the development of certain cancers. This research aims to understand some of the mechanisms involved in the diabetes-cancer overlap by focusing on the tumour-suppressor gene (CDKN2A/B)(p16) where the evidence for this overlap is the greatest. The case for focussing on the CDKN2A/B genes comes from genome wide association study data and rodent models: CDKN2A/B (p16) were the closest protein-coding genes to one of the novel Type 2 diabetes susceptibility loci uncovered by the

GWAs; secondly, rodent studies show that CDKN2A (p16) over expression leads to the diabetes phenotype.
The work outlined in this research protocol will help us to understand some of the fundamental processes involved in both diabetes and cancer. It could improve clinical care by uncovering new therapeutic targets to manipulate beta-cell function for the treatment of diabetes as well as providing information on the potential oncogenic side-effects of manipulating some of these disease processes.

**Study objective**

·To perform clinical studies that assess glucose tolerance in individuals with cancer-predisposing mutations in the CDKN2A gene (p16)(causing familial melanoma)

**Study design**

The carriers of a CDKN2A (p16)-mutation will be invited for an oral glucose tolerance test

This is a standard procedure undertaken by the chief investigator and the research nurses at the Department of Endocrinology routinely; thus there is vast amount of experience with these particular metabolic tests.

Subjects can consent to each test as they wish and can withdraw from any part of the study at any time. If subjects wish to withdraw then stored biological samples will be discarded and any coded link to clinical data will be removed.

Numbers to be recruited: 20 with predisposing CDKN2A (p16) mutations and 20 controls (partners or relatives without a CDKN2A (p16)-mutation). The sample size estimate is based on experience from equivalent studies but the potential exists to increase sample size through collaboration with other groups (and would be the subject of separate ethics applications).
Potential benefit to patients: recruited subjects may benefit from taking part in the study by learning of glucose tolerance abnormalities, *pre-diabetes* , that might otherwise not be tested for and diagnosed.

Protocol for OGTT sample collection and analysis:
·Participant attends the Department of Endocrinology 08:30 after 10 hour overnight fast, subjects have been able to drink water
·Baseline clinical characteristics are collected: age, weight (Kg), height (cm) and waist circumference
·A small intravenous cannula is placed in one antecubital vein to avoid multiple venepunctures
·Baseline bloods are drawn for glucose and insulin
·Participant is asked to drink a standard 75g oral glucose drink over 2-3mins

·Blood sample then collected at 15*, 30*, 60*, 90*and 120min after oral glucose drink to be analysed for glucose and insulin.
·Glucose samples are collected in 5ml grey fluoride oxalate vacutainer tubes: samples for insulin are collected in 7ml orange serum collection vacutainer tubes
·All samples are kept on ice and spun within 5 min of collection in a portable centrifuge at 5000G for 3min
·2 X 1ml aliquots of separated serum are then kept on ice and stored in -80 freezers until batched for assay
·Participant is given a light breakfast at the end of the OGTT

**Study burden and risks**

The visit for an intravenous glucose tolerance test will last for 3.5 hours.The cannulation sites may bruise and there is a small risk of infection which will be minimised by the use of sterile procedures. Some pain will be experienced during the insertion of the cannulae,
Participants may benefit from taking part in the study by learning of glucose tolerance abnormalities,
'pre*diabetes', that might otherwise not be tested for and diagnosed.
There is no direct benefit to participants but they will benefit from a pre*diabetes test.

# Contacts

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# Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

carrier of a CDKN2A (p16) mutation and partners or relatives without a CDKN2A-mutation

### Exclusion criteria

Being unwell or unable to give informed consent. Patients with dabetes mellitus

## Study design

### Design

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|---|---|
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 08-10-2012 |
| Enrollment: | 40 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 01-06-2012 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL35826.058.11 |